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ENVINT-D-20-01309: Long-term exposure to air pollution, road traffic noise, residential greenness, and prevalent and incident metabolic syndrome: Results from the population-based KORA F4/FF4 cohort in Augsburg, Germany

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ABSTRACT

Background: A growing number of epidemiological studies show associations between environmental factors and impaired cardiometabolic health. However, evidence is scarce concerning these risk factors and their impact on metabolic syndrome (MetS). This analysis aims to investigate associations between long-term exposure to air pollution, road traffic noise, residential greenness, and MetS.

Methods: We used data of the first (F4, 2006–2008) and second (FF4, 2013–2014) follow-up of the population-based KORA S4 survey in the region of Augsburg, Germany, to investigate associations between exposures and MetS prevalence at F4 (N = 2883) and MetS incidence at FF4 (N = 1192; average follow-up: 6.5 years). Residential long-term exposures to air pollution – including particulate matter (PM) with a diameter < 10 μm (PM_{10}), PM < 2.5 μm ($PM_{2.5}$), PM between 2.5 and 10 μm (PM_{coarse}), absorbance of $PM_{2.5}$ ($PM2.5_{abs}$), particle number concentration (PNC), nitrogen dioxide (NO_2), ozone (O_3) – and road traffic noise were modeled by land-use regression models and noise maps. For greenness, the Normalized Difference Vegetation Index (NDVI) was obtained. We estimated Odds Ratios (OR) for single and multi-exposure models using logistic regression and generalized estimating equations adjusted for confounders. Joint Odds Ratios were calculated based on the Cumulative Risk Index. Effect modifiers were examined with interaction terms.

Results: We found positive associations between prevalent MetS and interquartile range (IQR) increases in PM_{10} (OR: 1.15; 95% confidence interval [95% CI]: 1.02, 1.29), $PM_{2.5}$ (OR: 1.14; 95% CI: 1.02, 1.28), PM_{coarse} (OR: 1.14; 95% CI: 1.02, 1.27), and $PM_{2.5}$abs (OR: 1.17; 95% CI: 1.03, 1.32). Results further showed negative, but non-significant associations between exposure to greenness and prevalent and incident MetS. No effects were seen for exposure to road traffic noise. Joint Odds Ratios from multi-exposure models were higher than ORs from models with only one exposure.

Abbreviations: 33CCHS, 33 Communities Chinese Health Study; BMI, body mass index; CI, confidence interval; CRI, Cumulative Risk Index; DAG, directed acyclic graph; dB, decibel; GEE, generalized estimating equation; HDL, high-density lipoprotein; HNR Study, Heinz Nixdorf Recall Study; HR, hazard ratio; IDF, International Diabetes Federation; IQR, interquartile range; JOR, joint odds ratio; LUR model, land-use regression model; MetS, metabolic syndrome; N, number; NDVI, Normalized Difference Vegetation Index; NO_2, nitrogen dioxide; O_3, ozone; OR, Odds Ratio; PM, particulate matter; PM_{10}, PM with aerodynamic diameter < 10 μm; $PM_{2.5}$, PM with aerodynamic diameter < 2.5 μm; PM_{coarse}, PM with aerodynamic diameter 2.5–10 μm; $PM_{2.5}$abs, absorbance of $PM_{2.5}$; PNC, particle number concentration; SD, standard deviation; WHR, waist-to-hip ratio.

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1. Introduction

Metabolic syndrome (MetS) is considered to be a severe public health problem. The International Diabetes Federation (IDF) estimates that 20–25% of adults worldwide suffer from MetS (IDF, 2006), with increasing prevalence during the last decades (O'Neill and O'Driscoll, 2015). While various definitions for MetS exist, the internationally most accepted one is the consensus definition from 2009. It describes MetS as the presence of three or more of the following five criteria: elevated waist circumference, elevated fasting glucose, elevated fasting triglycerides, elevated systolic blood pressure or diastolic blood pressure, and decreased high-density lipoprotein (HDL) cholesterol levels (Alberti et al., 2009).

MetS significantly increases the risk of cardiovascular diseases and diabetes mellitus type 2 (Kaur, 2014; Grundy, 2008), two of the main causes of death globally (Foreman et al., 2018). This highlights the importance of understanding the factors that contribute to the development of MetS to prevent these diseases. While adiposity and a sedentary lifestyle are considered to be major risk factors (O'Neill and O'Driscoll, 2015; Alberti et al., 2009), a growing epidemiological evidence suggests that environmental risk factors like air pollution, traffic noise, and a lack of greenness play a role in the development of MetS and its related diseases. Air pollution, mainly particulate matter (PM), has been found to be associated with an increased risk of MetS: In the 33 Communities Chinese Health Study (33CCHS), the Odds Ratio (OR) for prevalent MetS per 10 $\mu g/m^3$ increase in PM_{10} was 1.13 (95% CI: 1.08; 1.19) and 1.09 (95% CI: 1.00; 1.18) for $PM_{2.5}$ (Yang et al., 2018). In Germany, the Heinz Nixdorf Recall (HNR) Study observed a significant positive association between prevalent MetS and an IQR increase in NO_2 (OR: 1.12; 95% CI: 1.02; 1.24) (Matthiessen et al., 2018). Results from other studies support these findings (Lee et al., 2019; Wallwork et al., 2017; Eze et al., 2015).

There is also evidence of associations between air pollution and adverse health outcomes linked to MetS. These include hypertension (Yang et al., 2018; Giorgini et al., 2016), type 2 diabetes mellitus (Eze et al., 2015; Liu et al., 2019), and increased cardiovascular mortality (Pope et al., 2015). However, it is still uncertain to which amount single air pollutants may contribute to the elevated risk of MetS, the impact of the exposure mixture, and which subgroups might be more susceptible to these effects.

Studies have found associations between road traffic noise and elevated waist circumference (Christensen et al., 2015), diabetes (Sorensen et al., 2013) and hypertension (van Kempen and Babisch, 2012). However, to our knowledge, evidence is lacking concerning a potential association between road traffic noise and MetS itself. Residential greenness seems to be linked to various positive health outcomes including a decreased risk for type 2 diabetes mellitus, and hypertension, as well as higher HDL cholesterol levels (Twohig-Bennett and Jones, 2018). The 33CHS and Whitehall II study found a negative association between MetS and residential greenness (Yang et al., 2020; de Keijzer et al., 2019). Furthermore, in one cross-sectional study higher percentages of parks in the neighborhood resulted in a decrease in a MetS risk score (Dengel et al., 2009).

This study aims to investigate the associations between long-term exposure to air pollutants, road traffic noise, and residential greenness with prevalent and incident MetS. We hypothesized that air pollution, road traffic noise, and residential greenness might be associated with risk for MetS. We employed multi-exposure models to assess whether the effects of the exposures were independent and estimated Joint Odds Ratios (JORs) from these models. Furthermore, we did subgroup analyses, investigating potential effect modifiers.

2. Methods

2.1. Study population

We used data from the first (F4) and second (FF4) follow-up of the prospective population-based KORA (Cooperative Health Research in the Region of Augsburg) baseline survey S4 in the region of Augsburg, Germany. KORA S4 took place in 1999–2001. For the survey, 4261 participants were recruited out of a randomized two-stage cluster sample with equal strata by sex and age from the target population of all German residents in the study region aged 25–74 years. KORA F4, the first follow-up to S4, was conducted in 2006–2008 and consisted of 3080 participants. For the second follow-up KORA FF4 in 2013/2014, 2279 participants were investigated. At baseline and follow-ups, physical examination and standardized interviews were performed with participants, and blood samples were collected. Study design, sampling methods, and data collection have been described in more detail elsewhere (Rathmann et al., 2000; Holle et al., 2005). All study participants gave written informed consent. KORA S4 and its follow-ups were approved by the Ethics Committee of the Bavarian Medical Association.

As data on triglyceride levels, glucose levels, and MetS were obtained only for a subgroup of participants aged 55–74 years at the baseline survey S4, we restricted our analysis to the first follow-up F4 for the cross-sectional analysis and additionally to the second follow-up FF4 for

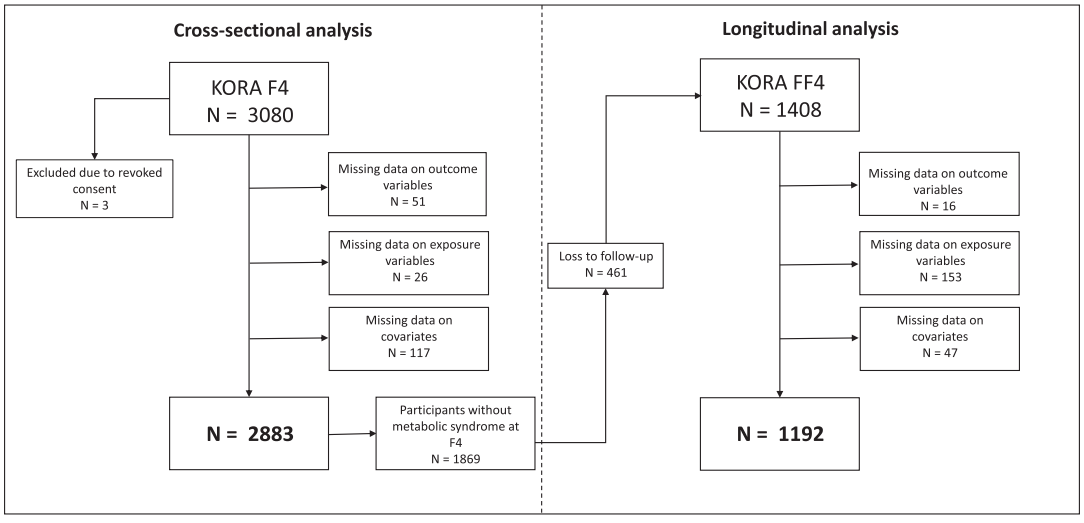


Fig. 1. Selection of study population for prevalent metabolic syndrome in the cross-sectional analysis at KORA F4 (N = 2883) and incident metabolic syndrome in the longitudinal analysis from KORA F4 to KORA FF4 (N = 1192).

the longitudinal analysis. The process of population selection for the main analysis can be found in Fig. 1. Of the 3080 subjects who had originally participated at the first follow-up (KORA F4), three had been deleted from the data because of revoked consent (N = 3). We excluded participants in case of missing data concerning MetS and its components (N = 51), at least one of the confounder variables (sex, age, physical activity, smoking status, alcohol consumption, family status, employment status, equivalent income, history of myocardial infarction, history of stroke; N = 117) or in case of any missing data in one of the exposure variables (N = 26). This left a sample of 2883 subjects for the cross-sectional analysis (prevalence of MetS). Of these, we selected all participants who had no prevalent MetS for the longitudinal analysis (incidence of MetS, N = 1869). Loss to follow-up for the second follow-up KORA FF4 was N = 461. After excluding subjects with missing data on outcome (N = 16), exposure (N = 153), and confounding variables (N = 47), there were N = 1192 subjects available for the analysis of incident MetS. Similarly, for the longitudinal analysis of each single component of MetS, we excluded prevalent cases of this single component at the time of KORA F4. Therefore, we included N = 946 for elevated blood pressure, N = 1421 for lowered HDL cholesterol level, N = 1339 for elevated triglyceride levels, N = 595 for elevated waist circumference and N = 1200 for elevated fasting glucose.

2.2. Outcome definition

Metabolic syndrome was defined according to the consensus definition from 2009 as presence of at least three of the following five criteria: waist circumference $\geq$ 94 cm in men or $\geq$ 80 cm in women; fasting glucose $\geq$ 5.6 mmol/l and/or use of glucose-lowering medication; systolic blood pressure $\geq$ 130 mmHg and/or diastolic blood pressure $\geq$ 85 mmHg and/or use of antihypertensive medication in a patient with a prior history of hypertension; fasting triglycerides $\geq$ 1.7 mmol/l and/or use of fibrates and/or nicotinic acid; high-density lipoprotein cholesterol $<$ 1.0 mmol/l in men or $<$ 1.3 mmol/l in women and/or use of fibrates and/or nicotinic acid (Alberti et al., 2009).

Data on outcome variables was gathered by trained investigators from 2007 to 2008 for the first follow-up (F4) and 2013–2014 for the second follow-up (FF4); blood pressure with a HEM 705 CP ambulatory blood pressure unit. Blood samples were taken after an overnight fast of at least 8 h. Glucose, HDL cholesterol and triglyceride level measurement methods differed between KORA F4 and FF4. In F4, serum glucose was analyzed using a hexokinase method (GLU Flex, Dade Behring, Deerfield, IL, USA). HDL cholesterol was measured in fresh serum by an enzymatic method (CHOL Flex and AHDL Flex, Dade Behring, Marburg, Germany). Triglycerides were measured in fresh serum with the GPO-PAP method (Dade Behring, Germany). In FF4, glucose concentrations were measured in fresh serum by an enzymatic, colorimetric method using the GLU assay on a Dimension Vista 1500 instrument (Siemens Healthcare Diagnostics Inc., Newark, USA) or using the GLUC3 assay, on a Cobas c702 instrument (Roche). HDL cholesterol and triglycerides were measured in serum using enzymatic, colorimetric methods from either Siemens (Siemens Healthcare Diagnostics Inc., Newark, USA) or Cobas (Roche Diagnostics GmbH, Mannheim, Germany), as the assays and instruments were changed during the study. A calibration between the two methods was performed using 122 samples from KORA FF4. In these participants, measurements were made with both instruments, and an appropriate formula was developed to calibrate the Roche measurements to the Siemens measurements. Further detail on the calibration process has been given elsewhere (Kowall et al., 2017).

2.3. Exposure measurement

2.3.1. Air pollution

Residential annual mean exposure to air pollution was modeled as part of the ULTRA III project (Environmental Nanoparticles and Health: Exposure, Modeling and Epidemiology of Nanoparticles and their Composition). The process has been described in detail elsewhere (Wolf et al., 2017). There was a total of 20 measurement locations within the study region, twelve being located within the city of Augsburg, eight in the two adjacent counties Augsburg and Aichach-Friedberg. Three bi-weekly measurements were conducted from March 2014 to April 2015 to cover the warm, intermediate and cold season. Simultaneously, measurements were also taken at a reference site throughout the whole measurement period to adjust for temporal variation. Measured air pollutants were PM $<$ 10 μm (PM_{10}), PM $<$ 2.5 μm ($PM_{2.5}$), PM 2.5-10 μm (PM_{coarse}), absorbance of $PM_{2.5}$ ($PM_{2.5}$abs), particle number concentration (PNC), nitrogen dioxide (NO_2), and ozone (O_3). Residential annual exposure to air pollution was assigned to the home addresses of each study participant as residential mean concentration by land-use regression models based on the standardized ESCAPE (European Study of Cohorts for Air Pollution Effects) approach (Eeftens et al., 2012). For the LUR models, linear regression models were calculated using the average concentration at the monitoring sites and potential predictor variables. These included local land use, building, population and household density, topography and road network data. The model fit of these LUR models has been described by Wolf et al. (Eeftens et al., 2012). R^2 values can be found in Supplemental Table 2.

2.3.2. Road traffic noise

Long-term road traffic noise was modeled by the company ACCON GmbH by drawing noise maps with the noise- and air-pollution information system LLIS (*Lärm- und Luftschadstoff-Informationssystem*, http://www.laermkarten.de/augsburg/), which provides a three-dimensional ground level of Augsburg. ACCON used traffic data from the year 2009 for the models. Information on ground plan, occupancy, height and reflection characteristics of around 87,000 buildings were taken into account. Roads were described with width, type, road surface and traffic volume including frequency of heavy goods vehicles of 2.8 metric tons. Noise levels were calculated four meters above the ground and were allocated to the home address of the participants. If the home address did not correspond to a building available in LLIS, the address was assigned to the nearest building. For rural participants, ACCON referred to a network of roads generated using georeferenced pictures form Google earth and open-street map data. Data on speed limits and daily traffic counts originated from different dates between the years 2000 and 2011. Data were derived from the Bavarian Ministry of the Interior, Building, and Transport, the digital street map of Augsburg, several traffic censuses, and surveys. Traffic counts were estimated in case there was no data available. Maximum annual A-weighted equivalent day-evening-night (Lden, 24 h) continuous sound pressure levels (dB(A)) were derived at the home address of the study participants.

2.3.3. Residential greenness

Exposure to residential greenness was calculated via the Normalized Difference Vegetation Index (NDVI), an indicator of vegetation density. For these calculations, cloud-free Landsat 5 TM, Landsat 7 ETM, and Landsat 8 OLI satellite images were used at a resolution of 30 m from the Global Visualisation Viewer from the U.S. Geological Survey (https://earthexplorer.usgs.gov/). Each NDVI map of the Augsburg area for KORA was built by two pictures. The images used for the cross-sectional analysis were taken on 26.08.2007, at the time of the KORA F4 follow-up. For the longitudinal analysis, we additionally used images taken on 10.06.2014 to assess for greenness at the time of KORA FF4. Residential or neighborhood surrounding greenness was defined as the mean NDVI in a Euclidean 500 m buffer around the place of residence of each participant. Negative pixels were excluded from the calculated NDVI maps.

2.4. Covariates

Based on existing literature (Yang et al., 2018; Lee et al., 2019;

Wallwork et al., 2017; Eze et al., 2015), we designed a directed acyclic graph (DAG) using the software DaGitty (Textor et al., 2011) to identify minimal sufficient sets of covariates. The DAG can be found in Supplemental Figure 5. As we considered age and sex as relevant confounders that should be included into our model, we chose the following main model congruent to the DAG: age, sex, physical activity (> 2 h/week regularly, 1 h/week regularly, 1 h/week unregularly, no or almost no physical activity), smoking status (non-smoker, smoker), alcohol consumption (no: 0 g/day; moderate: men > 0 and < 40 g/day, women > 0 and < 20 g/day; high: men >= 40 g/day, women >= 20 g/day), employment status (full-time, part-time, low-paid or unregular employment, no employment), family status (living alone, living with partner), and equivalent income. The different categories for alcohol regarding men and women were selected based on prior research in KORA (Keil et al., 1997; Wellmann et al., 2004). Covariates for the cross-sectional analysis were assessed during KORA F4 (2006–2008). For the longitudinal analysis, we additionally used measurements of covariates taken during KORA FF4 (2013/2014). Socio-demographic covariates, lifestyle characteristics, and clinical treatments were based on self-reported information. Anthropometric measurements were conducted by trained investigators at the study center.

2.5. Statistical analysis

We used logistic regression in the cross-sectional analysis to investigate the associations between prevalent MetS and interquartile range (IQR) increases in each single exposure variable while adjusting for potential confounders during the time of KORA F4. For the longitudinal analysis, we used generalized estimating equations (GEE) with a logit-link to assess the associations between exposure variables and incident MetS while adjusting for time-varying covariates. This method was chosen, because we assumed that values between the two measuring points for the variables in our model might not be independent. The chosen Working Correlation for the GEE was “compound symmetry”.

Participants with missing data on the outcome variables, covariates, or exposure variables were excluded from the analysis. As exposure variables we selected: residential mean averages of $PM_{2.5}$abs, PM_{coarse}, NO_2, PM_{10}, $PM_{2.5}$, PNC, O_3, and road traffic noise; exposure to residential greenness was assessed within a 500 m buffer around the residents’ homes.

Selected covariates were added stepwise to the model. First, we included basic individual characteristics variables for model 1 (age, sex). For model 2, lifestyle-related variables were added (physical activity, smoking status, alcohol consumption). Model 3, our main model, comprised further socioeconomic covariates (employment status, family status, equivalent income). Model 3 was also used to calculate associations for the five single components of the metabolic syndrome. As ORs tend to show higher values in cases where the outcome is frequent, we additionally estimated RRs for MetS using log-binomial Poisson regression with robust standard errors in the cross-sectional analysis and GEE with Poisson distribution in the longitudinal analysis.

We used multi-exposure models to assess the independent effects of the exposures for the cross-sectional analysis. Using our main model, we calculated two-exposure models for all combinations of exposure variables with a Spearman correlation coefficient =< 0.7. Furthermore, we examined effect estimates for $PM_{2.5}$, $PM_{2.5}$abs, and greenness within lower and higher strata (<= median vs. > median) of the other exposure variables to look for combined effects. We combined $PM_{2.5}$, O_3, road traffic noise, and residential greenness in models containing three or four exposure variables.

Assuming additive effects of single environmental exposures on the risk of MetS, we used the Cumulative Risk Index (CRI) method to calculate Joint Odds Ratios (JOR) to estimate combined effects of decreased residential greenness and elevated $PM_{2.5}$, O_3, and road traffic noise. This method has been used by Lippmann et al. to assess the combined risks of environmental exposures on health outcomes (Lippmann et al., 2013) and was developed further by other authors. Congruent with the definition by Jerret et al. (Jerrett et al., 2013); Crouse et al. (Crouse et al., 2015), and Klompmaker et al. (Klompmaker et al., 2019), we denote the JOR based on the combination of the p environmental exposures as the CRI and define it as:

$$CRI = exp\left[\sum_{p=1}^{p} \widehat{\beta}_p x_p\right] = exp(\widehat{\beta}^{'} x) = \prod_{p=1}^{p} JOR_p$$

where $\widehat{\beta}^{'} = \left(\widehat{\beta}_1 \ldots \widehat{\beta}_p\right)$ are the log odds ratios estimated in a model including all p environmental exposures. x’ = (x_1, … , x_p) are the levels at which each OR is evaluated, in our case an increase in IQR. Corresponding to Klompmaker et al. (Klompmaker et al., 2019), we define the 95% CI as:

$$95\%\ \text{CI} = \exp(\widehat{\beta}^{'} x) = \prod_{p=1}^{p} \text{JOR}_p$$

For estimating JORs, we reversed the direction of the association between residential greenness and MetS compared to the other analyses. Therefore, the JOR is defined as OR for an IQR increase in air pollution and road traffic noise and an IQR decrease in residential greenness compared to no increase (decrease in case of greenness) in all exposures.

Potential effect modifications had been identified by literature review and were investigated by adding interaction terms to the main model: sex (male vs. female), age (<= 65 years vs. > 65 years), physical activity (< 1 h vs. per week regularly vs. at least 1 h per week regularly), smoking (nonsmoker vs. smoker), diabetes (no prevalent diabetes vs. prevalent diabetes), obesity (BMI <= 30 kg/m^2 vs. BMI > 30 kg/m^2), and living area (city vs. town/suburb vs. rural).

Results are presented as Odds Ratios (OR) and Risk Ratios (RR) together with corresponding 95% confidence intervals (95% CI). The complete statistical analysis was performed using the software R, Version 3.4.3.

2.6. Sensitivity analysis

We conducted several sensitivity analyses to test the robustness of our results: (1) we excluded all participants who had moved since survey S4. For the cross-sectional analysis, we therefore excluded all participants who had changed their address between S4 and F4, and for the longitudinal analysis all who had moved between S4 and FF4; (2) we added the percentage of households with an estimated income below 1250 Euro within a 500 m × 500 m grid to the model to adjust for the socioeconomic status of the neighborhood; (3) we adjusted for smoking with pack years instead of smoking status; (4) we adjusted for body mass index (BMI) in the main model; (5) we further investigated deviation from linearity of the exposure–response functions visually by plotting the results of logit-link generalized additive models for the cross-sectional analysis and logit-link generalized additive mixed models for the longitudinal analysis using the covariates of the main model. (6) To test the robustness of the results of the longitudinal analysis, we calculated associations between exposure variables and incident MetS with a logit-link generalized linear mixed-effects model. (7) To investigate a potential selection bias in our longitudinal analysis, we adjusted for MetS at KORA F4 when estimating the association between prevalent MetS at KORA FF4 and environmental exposures.

3. Results

3.1. Study population

A detailed description of the populations for the cross-sectional and the longitudinal analysis can be found in Table 1. At the time of F4, 1014 participants had prevalent metabolic syndrome (35.2%), 1869 had no metabolic syndrome (64.8%). Subjects had an average age of 56.2 years

Table 1
Description of population for cross-sectional analysis at KORA F4 and longitudinal analysis at KORA FF4; Participants with metabolic syndrome (MetS) at baseline were excluded for the longitudinal analysis.

		F4			FF4	
	Total	**With MetS**	**Without MetS**	**Total**	**With MetS**	**Without MetS**
Item	N (%) or Mean ± SD	N (%) or Mean ± SD	N (%) or Mean ± SD	N (%) or Mean ± SD	N (%) or Mean ± SD	N (%) or Mean ± SD
Participants	2883 (100)	1014 (35.2)	1869 (64.8)	1192 (100)	216 (18.1)	976 (81.9)
Sex	Female: 1473 (51.1); Male: 1410 (48.9)	Female: 401 (39.5); Male: 613 (60.5)	Female: 1072 (57.4); Male: 797 (42.6)	Female: 667 (56.0); Male: 525 (44.0)	Female: 121 (44.0); Male: 95 (56.0)	Female: 572 (58.6); Male: 404 (41.4)
BMI (kg/m^2)	27.6 ± 4.8	30.6 ± 4.6	26.0 ± 4.1	26.6 ± 4.3	29.6 ± 4.4	26.0 ± 4.1
Age (years)	56.2± 13.1	62.0 ± 11.4	53.0 ± 13.0	59.1 ± 11.8	63.7 ± 10.7	58.0 ± 11.8
Waist-to-Hip-Ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Equivalent income (€)	1249 ± 597.3	1203 ± 581.0	1274 ± 604.7	1465 ± 660.8	1396 ± 615.2	1481 ± 669.8
Elevated blood pressure[1]	1413 (49.0)	868 (85.6)	545 (29.2)	434 (36.4)	178 (82.4)	256 (26.2)
Elevated triglyceride levels[2]	720 (25.0)	589 (58.1)	131 (7.0)	152 (12.8)	97 (44.9)	55 (5.6)
Decreased HDL[3]	571 (19.8)	409 (40.3)	162 (8.7)	49 (4.1)	31 (14.4)	18 (1.8)
Elevated fasting glucose[4]	956 (33.2)	756 (74.6)	200 (10.7)	377 (31.6)	186 (86.1)	191 (19.6)
Elevated waist circumference[5]	1971 (68.4)	973 (96.0)	998 (53.4)	822 (69.0)	212 (98.1)	610 (62.5)
Diabetes mellitus	328 (11.4)	294 (29.0)	34 (1.8)	52 (4.4)	22 (10.2)	30 (3.1)
Smoking status						
Nonsmoker	2378 (82.6)	882 (87.2)	1496 (80.0)	1007 (84.5)	181 (83.8)	826 (84.6)
Smoker	502 (17.4)	129 (12.7)	373 (20.0)	185 (15.5)	35 (16.2)	150 (15.4)
Physical activity						
> 2 h/week	713 (24.7)	205 (20.2)	508 (27.2)	357 (29.9)	49 (22.7)	308 (31.6)
1 h/week, regularly	877 (30.4)	279 (27.6)	598 (32.0)	397 (33.3)	70 (32.4)	327 (33.5)
1 h/week, unregularly	378 (13.1)	128 (12.6)	250 (13.4)	157 (13.2)	40 (18.5)	117 (12.0)
Non/almost non	915 (31.7)	402 (39.6)	513 (27.4)	281 (23.6)	57 (26.4)	224 (23.0)
Alcohol consumption[6]	14.4 ± 19.5					
No consumption	856 (29.7)	335 (33.0)	521 (27.9)	302 (25.3)	61 (28.2)	241 (24.7)
Moderate consumption	1523 (52.8)	495 (48.8)	1028 (55.0)	661 (55.5)	108 (50.0)	553 (56.7)
High consumption	504 (17.5)	184 (18.1)	320 (17.1)	229 (19.2)	47 (21.8)	182 (18.6)
Family status						
Living alone	690 (23.9)	236 (23.3)	454 (24.3)	291 (24.4)	55 (25.5)	236 (24.2)
Living with partner	2193 (76.1)	778 (76.7)	1415 (75.7)	901 (75.6)	161 (74.5)	740 (75.8)
Employment status						
Full time	1054 (36.6)	285 (28.1)	769 (41.1)	412 (34.6)	63 (29.2)	349 (35.8)
Part time	368 (12.8)	54 (5.3)	314 (16.8)	241 (20.2)	25 (11.6)	216 (22.1)
Low-paid/Unregular	170 (5.9)	44 (4.3)	126 (6.7)	77 (6.4)	14 (6.5)	63 (6.5)
None	1291 (44.8)	631 (62.2)	660 (35.3)	462 (38.8)	114 (52.8)	348 (35.7)
Myocardial infarction	91 (3.2)	64 (6.3)	27 (1.4)	20 (1.7)	10 (4.6)	10 (1.0)
Stroke	61 (2.1)	39 (3.8)	22 (1.2)	21 (1.8)	8 (3.7)	13 (1.3)
Living area						
City	1208 (41.9)	439 (43.3)	769 (41.1)	441 (37.0)	80 (37.0)	361 (37.0)
Town/Suburb	1198 (41.6)	405 (39.9)	793 (42.4)	539 (45.2)	93 (43.1)	448 (45.9)
Rural	477 (16.5)	170 (16.8)	307 (16.4)	212 (17.8)	43 (19.9)	167 (17.1)

[1] Diastolic blood pressure >= 85 mmHg and/or systolic blood pressure >=130 mmHg or intake of antihypertensiva with prehistory of hypertension
[2] Triglyceride levels >= 150 or intake of fibrates
[3] HDL levels < 40 men / <50 women or intake of fibrates
[4] fasting glucose >= 100 mg/dl or intake of glucose lowering medication
[5] waist circumference >= 94 cm men/ >= 80 cm women
[6] No consumption: 0 g/day; Moderate consumption: > 0 g/day and < 40 g/day for men and > 0 g/day and < 20 g/day for women; High consumption: > 40 g/day for men and > 20 g/day for women

Table 2
Description and Spearman correlation coefficients of annual air pollution concentrations, road traffic noise and greenness estimated at residence for the cross-sectional analysis (N = 2883).

Name	**Min**	**Median**	**Mean ± SD**	**IQR**	**Max**	**PM_{10}**	**$PM_{2.5}$**	**PM_{coarse}**	**$PM_{2.5}$ abs**	**PNC**	**NO_2**	**O_3**	**Road traffic noise**	**Green-ness**
PM_{10} (μg/m^3)	12.3	16.3	16.6± 1.5	2.1	22.3	1								
$PM_{2.5}$ (μg/m^3)	8.2	11.9	11.8± 1.0	1.4	14.4	0.52	1							
PM_{coarse} (μg/m^3)	2.5	4.9	5.0± 1.0	1.3	8.8	0.78	0.58	1						
$PM_{2.5}$abs (10^{-5}/m)	0.8	1.2	1.2± 0.2	0.3	1.8	0.77	0.62	0.81	1					
PNC (10^3/cm^3)	3.2	7.3	7.3± 1.8	2.0	15.7	0.81	0.65	0.76	0.77	1				
NO_2 (μg/m^3)	6.9	13.8	14.2± 4.5	6.9	27.5	0.72	0.72	0.84	0.86	0.77	1			
O_3 (μg/m^3)	32.1	39.2	39.1± 2.4	3.4	46.2	0.04	−0.19	0.11	−0.12	−0.04	−0.18	1		
Road traffic noise (dB)	22.3	53.7	54.6± 6.7	8.1	76.2	0.49	0.34	0.45	0.42	0.41	0.48	−0.10	1	
Greenness (NDVI)	0.1	0.3	0.3± 0.1	0.1	0.6	−0.67	−0.64	−0.72	−0.73	−0.73	−0.80	0.07	−0.33	1

Table 3
Association between residential environmental exposures and prevalent metabolic syndrome per interquartile range increase (IQR) in exposure for the cross-sectional analysis (N = 2883).

Exposure	Model 1[a]		Model 2[b]		Model 3 (Main Model)[c]		Model 3 (Main Model)[c]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	RR (95% CI)	P
PM_{10} ($\mu g/m^3$)	1.13 (1.01; 1.26)	0.04	1.12 (1.00; 1.26)	0.05	1.15 (1.02; 1.29)	0.02	1.08 (1.02; 1.15)	0.01
$PM_{2.5}$ ($\mu g/m^3$)	1.13 (1.01; 1.26)	0.04	1.13 (1.01; 1.27)	0.04	1.14 (1.02; 1.28)	0.02	1.08 (1.01; 1.15)	0.03
PM_{coarse} ($\mu g/m^3$)	1.11 (0.99; 1.23)	0.07	1.11 (0.99; 1.23)	0.07	1.14 (1.02; 1.27)	0.02	1.08 (1.01; 1.16)	0.02
$PM_{2.5}$abs (10^{-5}/m)	1.14 (1.00; 1.28)	0.04	1.13 (1.00; 1.28)	0.06	1.17 (1.03; 1.32)	0.02	1.09 (1.02; 1.17)	0.02
PNC ($10^3/cm^3$)	1.03 (0.94; 1.12)	0.57	1.02 (0.93; 1.12)	0.65	1.04 (0.95; 1.13)	0.42	1.02 (0.97; 1.08)	0.38
NO_2 ($\mu g/m^3$)	1.10 (0.97; 1.25)	0.13	1.10 (0.97; 1.25)	0.15	1.13 (0.99; 1.29)	0.06	1.07 (1.00; 1.15)	0.05
O_3 ($\mu g/m^3$)	1.00 (0.88; 1.12)	0.93	1.01 (0.90; 1.14)	0.85	1.01 (0.90; 1.14)	0.83	1.01 (0.94; 1.07)	0.83
Road traffic noise (dB)	1.05 (0.96; 1.16)	0.29	1.05 (0.95; 1.16)	0.36	1.06 (0.95; 1.17)	0.29	1.03 (0.97; 1.09)	0.30
Greenness (NDVI)	0.96 (0.86; 1.07)	0.48	0.97 (0.87; 1.08)	0.52	0.95 (0.84; 1.06)	0.32	0.97 (0.91; 1.03)	0.30

[a] exposure + age, sex.
[b] Model 1 + physical activity, alcohol consumption, smoking status.
[c] Model 2 + family status, equivalent income, occupational status.

and an average BMI of 27.6 kg/m^2. The prevalence of single MetS components was 49.0% for elevated blood pressure (N = 1413), 25.0% for elevated triglyceride levels (N = 720), 19.8% for decreased HDL cholesterol levels (N = 571), 33.2% for elevated fasting glucose (N = 956) and 68.4% for elevated waist circumference (N = 1971).

For the longitudinal analysis, we included only subjects without MetS at the time of F4. These were on average younger (53.0 years) and had a lower BMI (26.0 kg/m^2) than those participants with MetS at F4 (age: 62.0 years, BMI: 30.6 kg/m^2). There were 216 cases of incident MetS (18.1%). The prevalence of single MetS components was 34.7% for elevated blood pressure (N = 464), 13.0% for elevated triglyceride levels (N = 174), 4.4% for decreased HDL cholesterol (N = 59), 31.0% for elevated fasting glucose (N = 415) and 67.3% for elevated waist circumference (N = 901).

3.2. Exposures

Descriptive statistics and Spearman correlation coefficients for air pollutants, road traffic noise and residential greenness for the cross-sectional analysis can be found in Table 2. Differences in the longitudinal analysis were negligible (Supplemental Table 1). Maxima for PM_{10} (22.3 $\mu g/m^3$) and PM_{25} (14.4 $\mu g/m^3$) exceeded the average annual mean concentrations of the WHO air quality guidelines (World Health Organization, 2005), while the maximum concentration of NO_2 (27.5 $\mu g/m^3$) did not. NO_2 was within the European limit value of an average maximum of 40 $\mu g/m^3$ per year (Directive 2008/50/EC). Air pollutants showed moderate to very strong correlations among each other; an exception was O_3, which was very weakly corelated with the other air pollutants. Road traffic noise showed weak to moderate correlations with the other exposures. Residential greenness was negatively correlated with the other exposure variables except for O_3 (r = 0.07).

3.3. Cross-sectional analyses

Results for prevalent MetS are presented in Table 3. We found positive association between prevalent MetS and IQR increases in PM_{10} (OR: 1.15; 95% CI: 1.02; 1.29), $PM_{2.5}$ (OR: 1.14; 95% CI: 1.02; 1.28), PM_{coarse} (OR: 1.14; 95% CI: 1.02; 1.27), and $PM_{2.5}$abs (OR: 1.17; 95% CI: 1.03; 1.32) in our main model (Model 3). We further found positive associations for NO_2 (OR: 1.13; 95% CI: 0.99; 1.29), PNC (OR: 1.04; 95% CI: 0.95; 1.13), O_3 (OR: 1.01; 95% CI: 0.90; 1.14) and road traffic noise (OR: 1.06; 95% CI: 0.96; 1.17), although they were not statistically significant. The same applies to residential greenness, which was negatively associated (OR: 0.95; 95% CI: 0.84; 1.06). Risk Ratios showed consistently smaller effects for all environmental exposures.

Results for the five MetS components can be found in Supplemental Table 3. Here, we found significant associations for lowered HDL cholesterol levels and $PM_{2.5}$abs (OR: 1.18; 95% CI: 1.02; 1.36) and for the associations between elevated triglyceride levels and $PM_{2.5}$abs (OR: 1.16; 95% CI: 1.02; 1.33), NO_2 (OR: 1.15; 95% CI: 1.01; 1.32), and residential greenness (OR: 0.86; 95% CI: 0.77; 0.97).

3.4. Longitudinal analyses

Results of the longitudinal analysis are shown on Table 4. For incident MetS, we found a positive, but non-significant association for an IQR increase in O_3 in model 3, our main model (OR: 1.18; 95% CI: 0.97; 1.45). There was a negative, but non-significant association for residential greenness (OR: 0.86; 95% CI: 0.71; 1.08). RRs did not differ noteworthy from these results.

Results of the longitudinal analysis for the five MetS components can be found in Supplemental Table 4. Here, we found significant negative associations between residential greenness and elevated blood pressure

Table 4
Association between residential environmental exposures and incident metabolic syndrome per interquartile range (IQR) increase in exposure for the longitudinal analysis (N = 1192).

Exposure	Model 1[a]		Model 2[b]		Model 3 (Main Model)[c]		Model 3 (Main Model)[c]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	RR (95% CI)	P
PM_{10} ($\mu g/m^3$)	0.98 (0.80; 1.20)	0.85	0.96 (0.79; 1.17)	0.69	0.96 (0.78; 1.18)	0.69	0.97 (0.81; 1.17)	0.72
$PM_{2.5}$ ($\mu g/m^3$)	1.01 (0.83; 1.23)	0.94	0.99 (0.81; 1.20)	0.88	0.98 (0.80; 1.20)	0.86	0.99 (0.83; 1.17)	0.87
PM_{coarse} ($\mu g/m^3$)	0.95 (0.79;1.15)	0.61	0.94 (0.78; 1.13)	0.49	0.93 (0.77; 1.13)	0.47	0.94 (0.80; 1.11)	0.49
$PM_{2.5}$abs (10^{-5}/m)	0.91 (0.74; 1.14)	0.42	0.89 (0.71; 1.11)	0.30	0.89 (0.71; 1.11)	0.29	0.90 (0.74; 1.10)	0.30
PNC ($10^3/cm^3$)	1.02 (0.88; 1.18)	0.78	1.01 (0.87; 1.16)	0.93	1.01 (0.87; 1.17)	0.93	1.01 (0.89; 1.15)	0.90
NO_2 ($\mu g/m^3$)	0.94 (0.77; 1.16)	0.59	0.91 (0.74; 1.13)	0.40	0.91 (0.73; 1.12)	0.37	0.92 (0.7;7 1.11)	0.39
O_3 ($\mu g/m^3$)	1.13 (0.93; 1.38)	0.22	1.18 (0.97; 1.45)	0.10	1.18 (0.97; 1.45)	0.10	1.16 (0.97; 1.38)	0.11
Road traffic noise (dB)	0.89 (0.74; 1.07)	0.22	0.88 (0.74; 1.06)	0.17	0.88 (0.74; 1.06)	0.18	0.90 (0.77; 1.05)	0.18
Greenness (NDVI)	0.84 (0.71; 1.00)	0.05	0.86 (0.72; 1.03)	0.10	0.86 (0.71; 1.03)	0.09	0.87 (0.75; 1.02)	0.09

[a] exposure + age, sex.
[b] Model 1 + physical activity, alcohol consumption, smoking status.
[c] Model 2 + family status, equivalent income, occupational status.

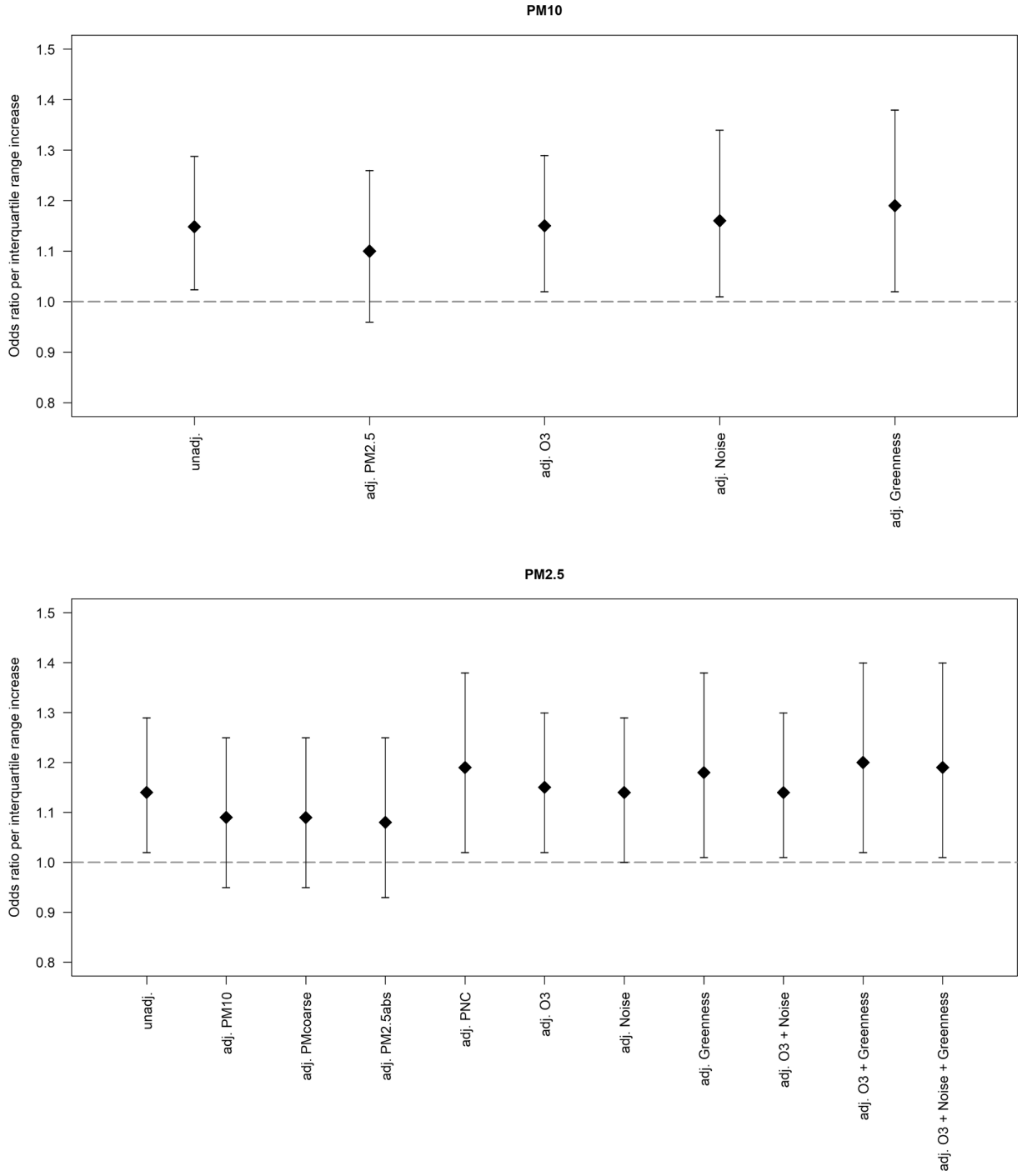


Fig. 2. Results of two-exposure models for PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5}$abs, and NO_2 in the cross-sectional analysis. Odds Ratios per interquartile range (IQR) increase in exposure for prevalent metabolic syndrome using the main model. *unadj.: adjusted with no second exposure additional to the main model; adj.: adjusted with a second exposure variable additional to the main model.*

(OR: 0.82; 95% CI: 0.68; 0.99), elevated fasting glucose (OR: 0.84; 95% CI: 0.73; 0.97), and elevated triglyceride levels (OR: 0.72; 95% CI: 0.59; 0.88).

3.5. Multi-exposure models

Results of multi-exposure models in the cross-sectional analysis can be found in Fig. 2. After adjusting for $PM_{2.5}$, effects for PM_{10}, PM_{coarse}, and $PM_{2.5}$abs were not significant anymore. Furthermore, we found stronger effects of $PM_{2.5}$ for lower levels of ozone and road traffic noise; residential greenness showed protective effects at lower levels of ozone (Supplemental Fig. 2). When combined with PM_{10} or $PM_{2.5}$, the association between greenness and MetS in models with two or more exposure variables reversed and was positive.

3.6. Joint odds ratios

JORs for $PM_{2.5}$, O_3, road traffic noise and residential greenness for

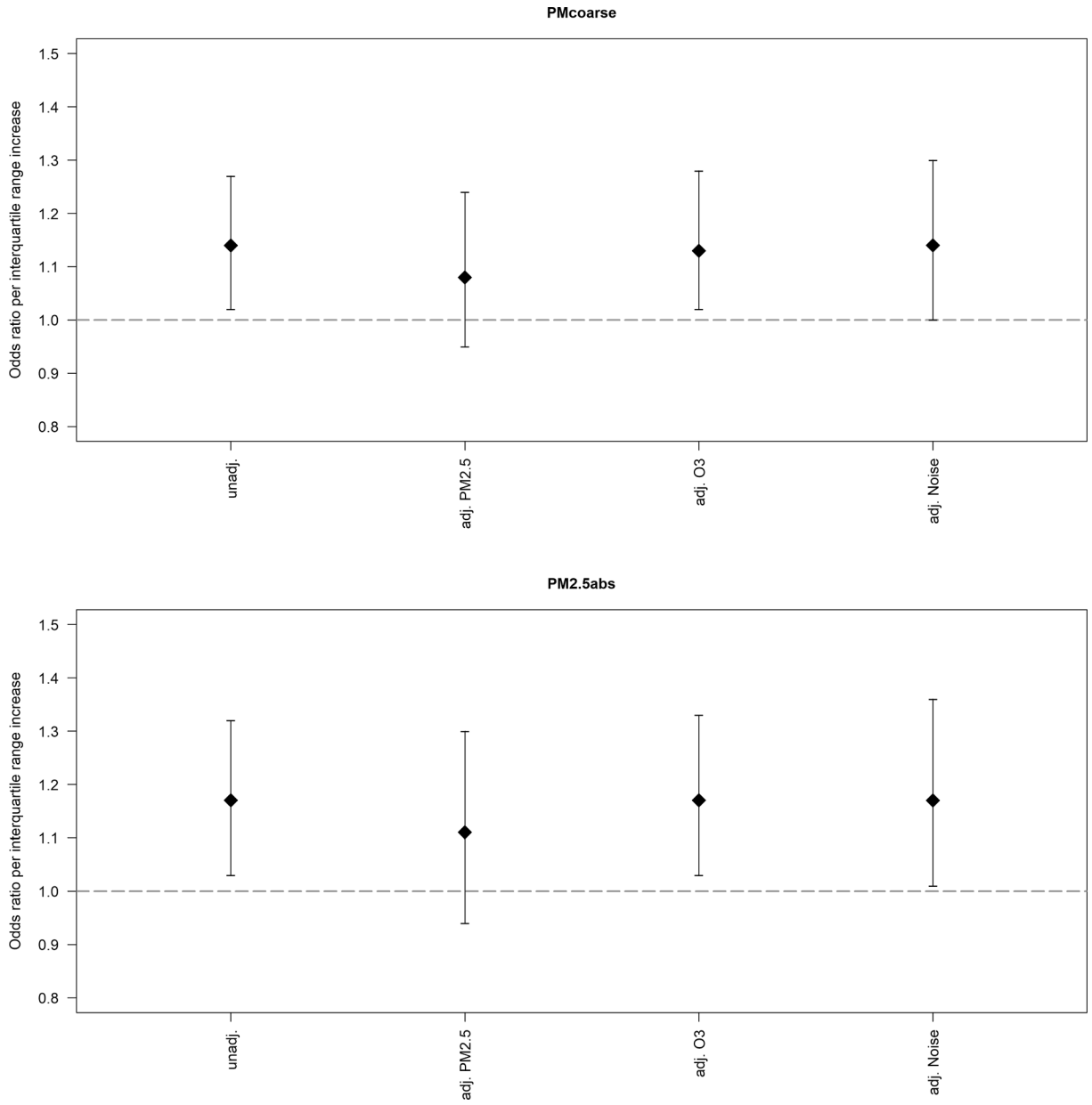


Fig. 2. (*continued*).

the association with prevalent MetS in the cross-sectional analysis can be found in Fig. 3. We found the highest JOR for an IQR increase in $PM_{2.5}$, O_3, and road traffic noise (OR: 1.21; 95% CI: 0.99; 1.47). JORs were usually higher than effects in the single-pollutant models of the investigated exposures. An exception was the JOR for an IQR increase in $PM_{2.5}$ and an IQR decrease in residential greenness (OR: 1.13; 95% CI: 0.99; 1.28), which was slightly smaller than the OR for $PM_{2.5}$ in a single-pollutant model (OR: 1.14; 95% CI: 1.02; 1.28).

3.6.1. *Effect modification*

Results of the analysis for effect modifications for prevalent MetS are presented in Fig. 4. Effects of $PM_{2.5}$ and $PM_{2.5}$abs were slightly stronger for men. ORs were higher for individuals with diabetes concerning $PM_{2.5}$. The area where participants lived was a statistically significant modifier of the association between MetS and residential greenness: While more surrounding greenness tended to show a protective effect for participants living in urban areas, it was a risk factor in rural areas.

Effect modifications for incident MetS in the longitudinal analysis can be found in Supplemental Fig. 1. Here, effects of air pollutants and the effect of residential greenness tended to be higher in men, whereas the effect of living area on the association between surround green and MetS directed into the opposite direction.

3.6.2. *Sensitivity analyses*

Adjusting for pack years instead of smoking status, including only participants who had not moved since baseline survey S4, and adding the socioeconomic status of the neighborhood to the model did not alter estimates noteworthy in the cross-sectional analysis, although estimates for NO_2 and $PM_{2.5}$ were not significant anymore after excluding participants who had moved since baseline survey S4 (Supplemental Table 6). In the longitudinal analysis, effect estimates stayed mostly constant (Supplemental Table 7). After including BMI to the main model, ORs generally increased. Thus, the association between prevalent MetS and NO_2 became significant in the cross-sectional analysis (OR: 1.17; 95% CI: 1.02; 1.35), whereas in the longitudinal analysis we found a significant effect for O_3 (OR: 1.32; 95% CI: 1.06; 1.63). Applying a generalized linear mixed-effects model did not change the associations between exposure variables and incident metabolic syndrome

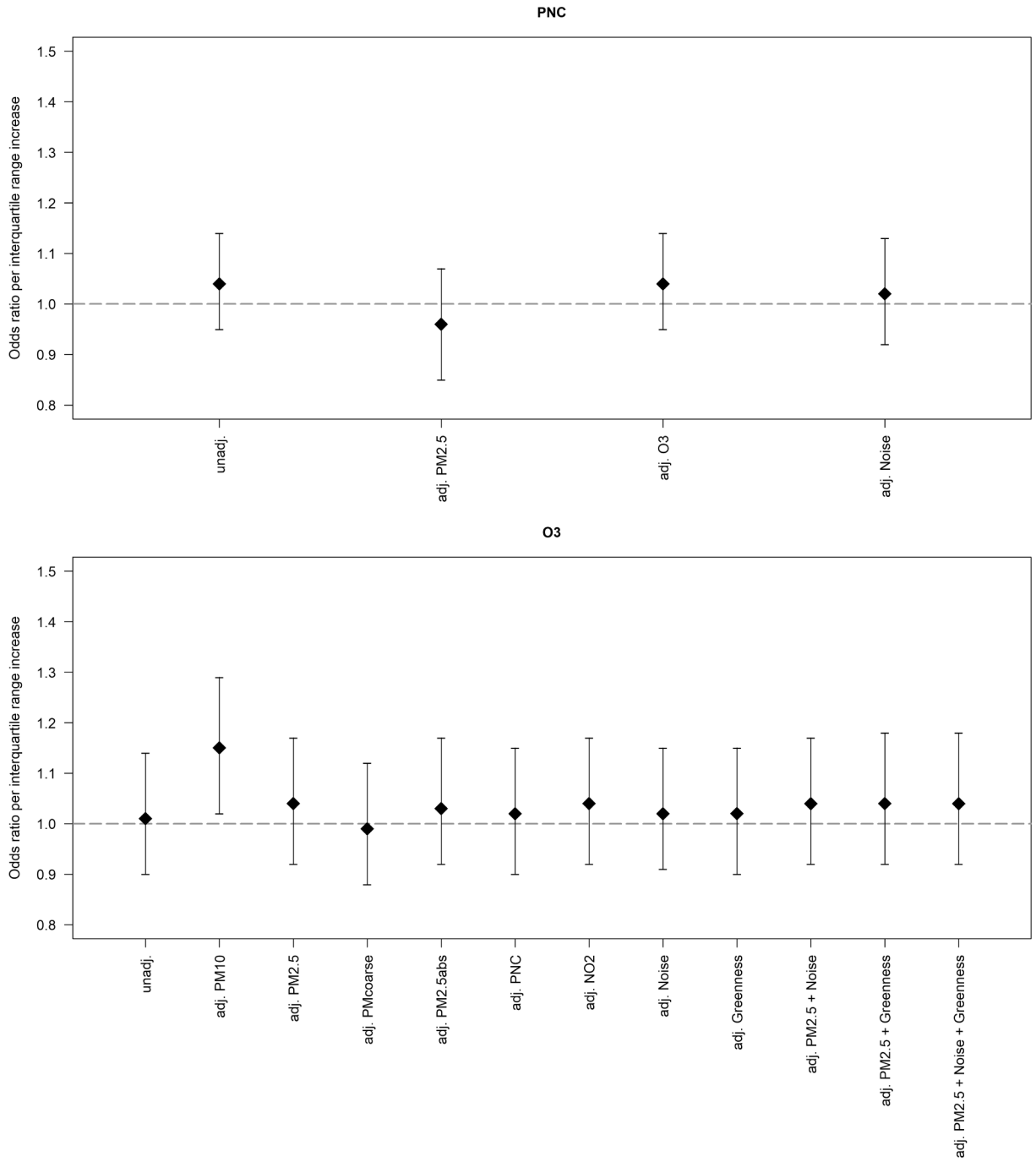


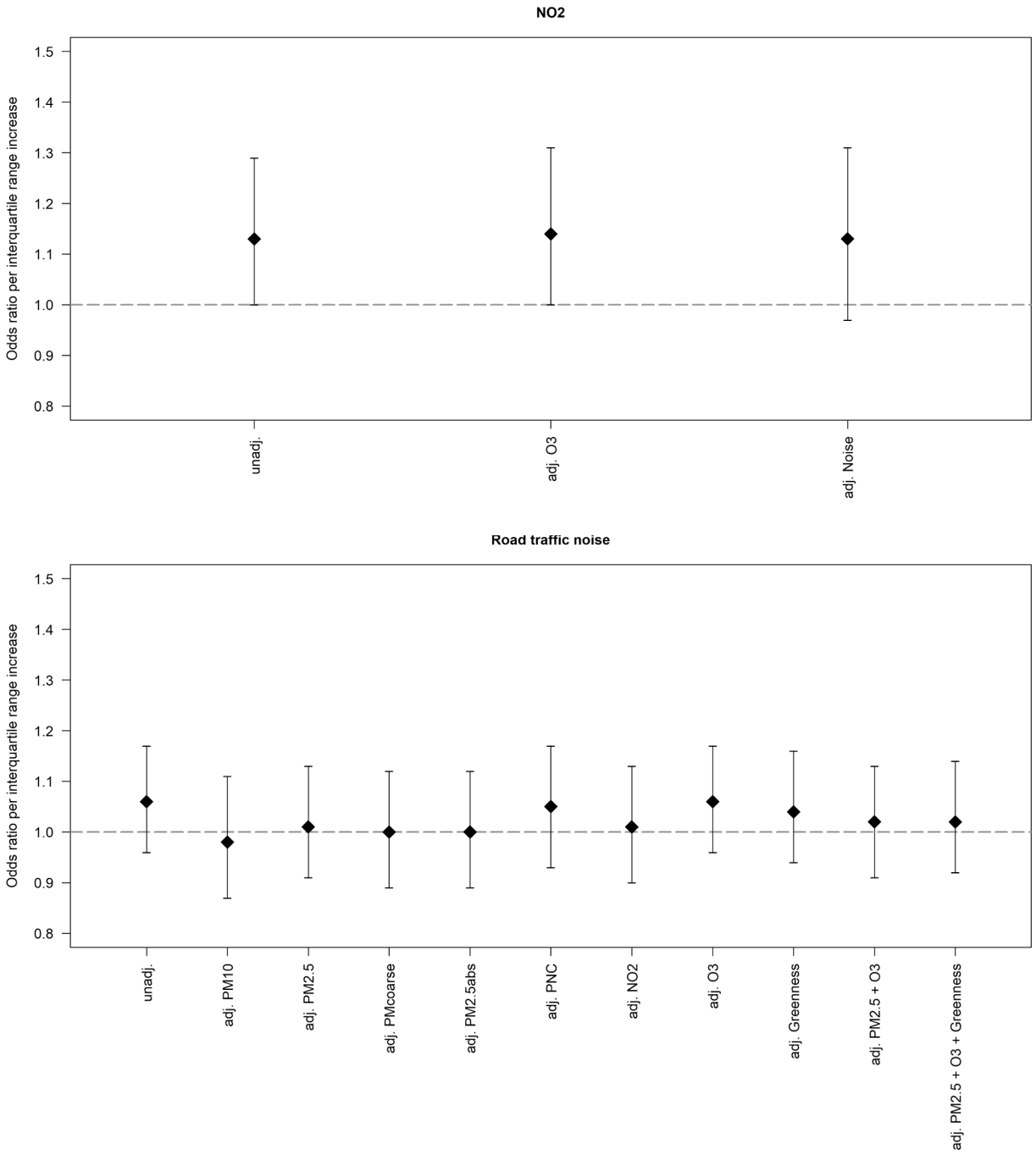
Fig. 2. (*continued*).

noteworthy. Visual inspection of the exposure–response functions suggested no major deviations from linearity for prevalent MetS (Supplemental Fig. 3) and incident MetS (Supplemental Fig. 4). Adjusting for MetS at KORA F4 when calculating the OR between prevalent MetS at KORA FF4, estimates remained mostly unchanged, with the exception of O_3, where the association with MetS became smaller than in the main analysis (OR: 1.05; 95% CI: 0.90; 1.22). Additionally, the effect of road traffic noise became statistically significant (OR: 0.87; 95% CI: 0.77; 0.99).

4. Discussion

4.1. Summary

In summary, our results suggest a positive association between an increase in PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5}$abs and prevalent MetS. For incident MetS, we found no significant associations. We saw no significant associations for road traffic noise; while the effect showed a positive association in the cross-sectional analysis, it was slightly negative in the longitudinal analysis. Residential greenness showed a negative association with MetS in both the cross-sectional and the longitudinal analysis, but neither was statistically significant. When adjusting for independent effects of the exposure variables, estimates for $PM_{2.5}$ and road traffic noise decreased in the cross-sectional analysis when including further



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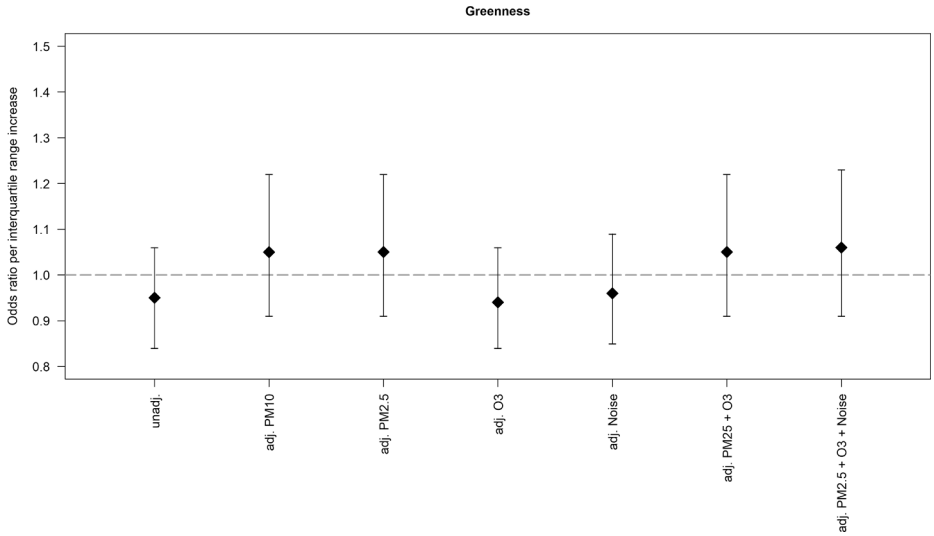
air pollutants in the model. We found no clear indications of susceptible population subgroups. JORs were higher than effects in single pollutant models.

4.2. Comparison to literature

4.2.1. Main analyses

In our cross-sectional analysis, we found positive associations for IQR increases in PM_{10}, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$abs with prevalent MetS. These results are consistent with previous findings. Studies investigating the associations between air pollution and MetS have mostly focused on PM. In the 33CCHS study, 10 μg/m^3 increases in PM_{10} and $PM_{2.5}$ were significantly associated with a higher chance for prevalent MetS, with ORs of 1.13 (95% CI: 1.08; 1.19) and 1.09 (95% CI: 1.00; 1.18), respectively (Yang et al., 2018). Further, the Heinz Nixdorf Recall (HNR) Study reported positive, but non-significant associations for an IQR increase in PM_{10} (OR: 1.02; 95% CI: 0.93; 1.11) and $PM_{2.5}$ (OR: 1.07; 95% CI: 0.94; 1.20) with prevalent MetS (8). This study took also place in Germany, had a comparable number of participants at baseline (N = 4457), and a similar follow-up time (5.1 years) as our study. However, the study population for the longitudinal analysis in the HNR Study had more than twice the size of our longitudinal analysis (N = 3074). Here, the HNR Study found positive, but borderline significant associations between an IQR increase in PM_{10} (OR: 1.14; 95% CI: 0.99; 1.32) and $PM_{2.5}$ (OR: 1.19; 95% CI: 0.98; 1.44) and incident MetS. Previous studies had found a significant association between $PM_{2.5}$ and incident MetS. In a Korean study with 119,998 participants, the Hazard Ratio (HR) for incident MetS per 10 μg/m^3 increase in $PM_{2.5}$ was 1.07 (95% CI: 1.03;



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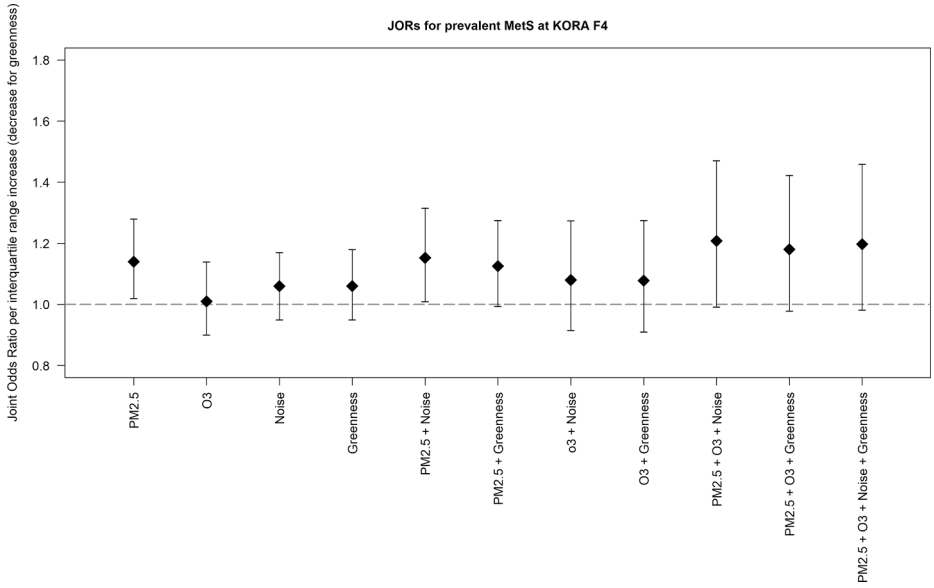


Fig. 3. Joint Odds Ratios for $PM_{2.5}$, O_3, Road traffic noise, and residential greenness from single, two-, and multi-exposure models using the Cumulative Risk Index. Joint Odds Ratios per interquartile range (IQR) increase in each exposure for prevalent metabolic syndrome using the main model.

1.11) (Lee et al., 2019); in the US-American Normative Aging Study, a 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an increased risk for incident MetS in an elderly male population (HR: 1.27; 95% CI: 1.06; 1.52) (Wallwork et al., 2017). For both PM_{10} and $PM_{2.5}$, we could not see these effects for the association with incident MetS.

$PM_{2.5}$abs and NO_2 are considered as markers for traffic-related air pollution. We found a positive association between an IQR increase in $PM_{2.5}$abs for prevalent, but not for incident MetS. In the HNR Study, findings showed no noteworthy effects of $PM_{2.5}$abs for both prevalent and incident MetS (Matthiessen et al., 2018). While the OR between an IQR increase in NO_2 and prevalent MetS showed an increased risk in our analysis, this association was not significant. Therefore, we failed to see an effect that has been shown in previous findings. The 33CCHS study reported a strong effect of a 10 $\mu g/m^3$ increase in NO_2 for the risk of prevalent MetS (OR: 1.33; 95% CI: 1.12; 1.57) (Yang et al., 2018). In the HNR Study, the association between an IQR increase in NO_2 and prevalent MetS showed a similar size compared to our analysis (OR: 1.12; 95% CI: 1.02; 1.24) (Matthiessen et al., 2018).

O_3 has been linked to an increased risk for cardiovascular death in epidemiological studies, but it is unclear whether these effects are dependent on other air pollutants (Turner et al., 2016; Jerrett et al., 2009). An IQR increase in O_3 was not associated with a higher risk for both prevalent and incident MetS in our main analysis. Therefore, we could not replicate the result from the 33CCHS study, where a significant positive association between an increase in O_3 and prevalent MetS was observed (OR: 1.10; 95% CI: 1.01; 1.18) (Yang et al., 2018). After adding BMI as a covariate to the main model in a sensitivity analysis, the association between O_3 and incident MetS became significant and was the strongest effect found in our analyses. This effect may be explicable by over-adjustment. However, it is unclear why the ORs for the other exposure variables were not affected comparably.

For road traffic noise, our analyses showed no consistent results. While to our knowledge no study before has investigated the effect of road traffic on MetS itself, several studies have found associations to health outcomes related to MetS: hypertension (van Kempen and Babisch, 2012), diabetes mellitus (Sorensen et al., 2013), and

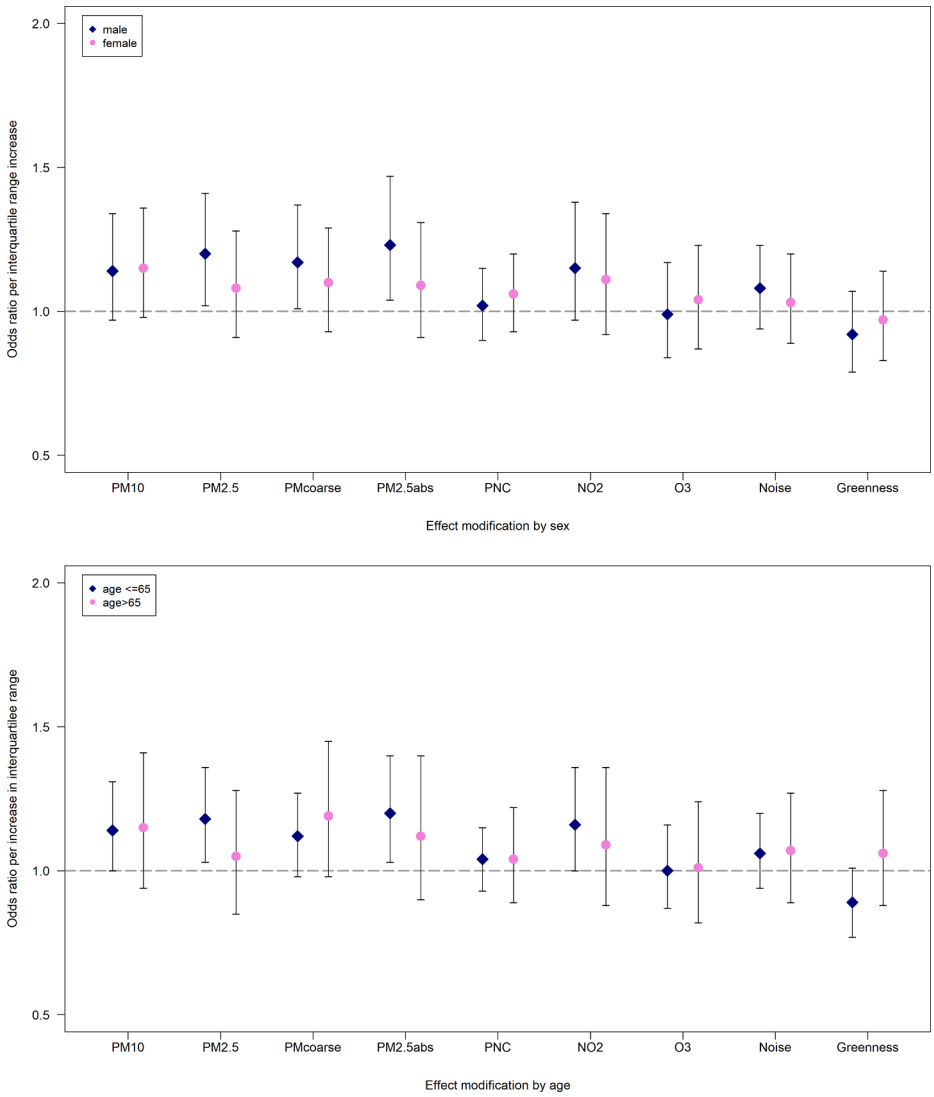


Fig. 4. Results of effect modification analysis for sex, age physical activity, smoking status, diabetes, obesity, and living area as effect modifiers for the cross-sectional analysis at KORA F4. Odds ratios per increase in interquartile range for prevalent metabolic syndrome using the main model.

myocardial infarction (Sorensen et al., 2012). However, our results for single components of MetS did not show clear trends as well.

Associations between residential greenness and MetS were negative in both the cross-sectional and the longitudinal analysis, but neither was significant. Therefore, we only found an indication of the protective effect for residential greenness that has been shown in previous analyses. An interquartile range increase in NDVI within a 500 m buffer was significantly associated with a decreased OR for MetS both in the 33CCHS (Yang et al., 2020) and in the Whitehall II study (de Keijzer et al., 2019). Furthermore, a cross-sectional study with 188 adolescents in the US found a significant negative association between a metabolic syndrome cluster score and the percentage of land used as parks (Dengel et al., 2009). Concerning single components of MetS, the 33CCHS study found living areas with higher amount of greenness linked to higher levels of HDL cholesterol and lower levels of triglycerides (Yang et al., 2019). While our results showed a significant protective effect of an IQR increase in residential greenness for both prevalent and incident elevated triglyceride levels, associations for HDL cholesterol were negative, though non-significant.

4.2.2. *Multi-exposure models*

Residential greenness did not lose its negative association with prevalent MetS when adjusted for ozone or road traffic noise. However, after adjusting for PM_{10} or $PM_{2.5}$, the association reversed and became positive. These results should be considered carefully, as residential greenness was strongly correlated with both PM_{10} and $PM_{2.5}$. For road traffic noise, the association with prevalent MetS diminished considerably after adjusting for particulate matter and NO_2. While this association has not been researched directly in previous studies, in a Californian cohort study the associations between MetS and both NO_x and noise remained unchanged when both exposures were added to the model (Yu et al., 2020).

JORs models using two or more exposures were higher than ORs based on single exposure models. Similar to previous findings, results of JORs indicate that considering environmental exposures separately may lead to miss-classifications regarding the risk attributable to these exposures. Combined effects of $PM_{2.5}$ and road traffic noise were mostly attributable to $PM_{2.5}$ in our models, while the JOR of ozone, road traffic noise, and greenness seemed to be constituted mostly by the latter two. Klompmaker et al. (Klompmaker et al., 2019) found higher JORs for decreased greenness and increased air pollution for diabetes, a cardiometabolic disease related to MetS, compared to single-exposure ORs. We found the same effect for MetS in our models when greenness was combined with O_3 and with both $PM_{2.5}$ and O_3. The JOR of increased

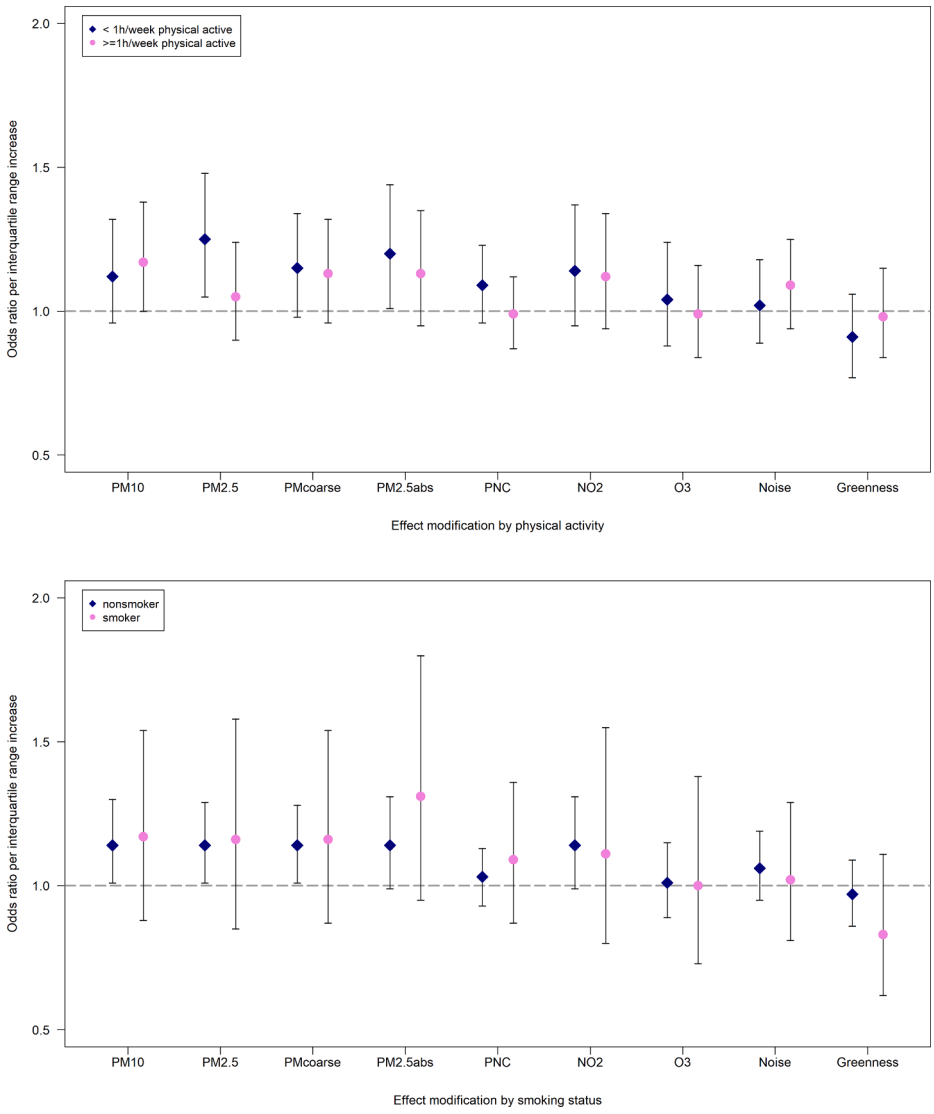


Fig. 4. (*continued*).

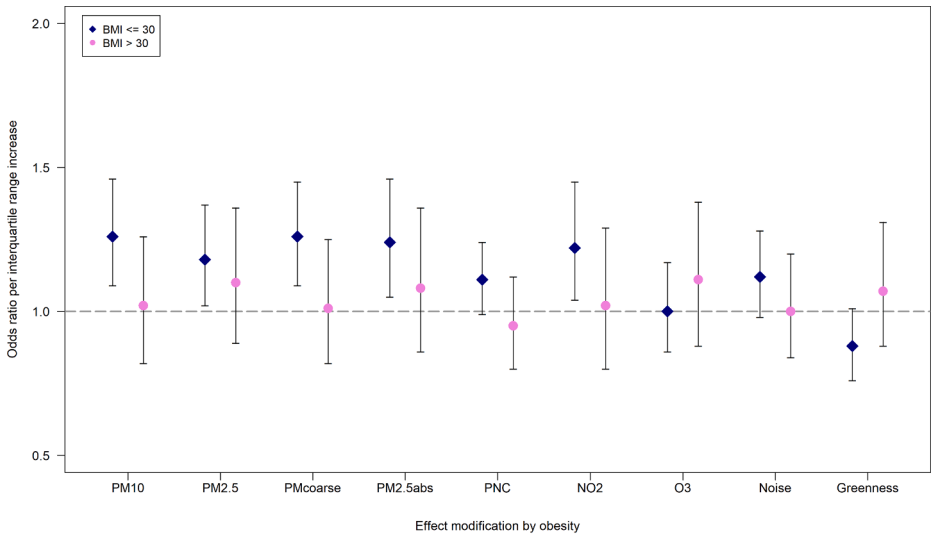
$PM_{2.5}$ and decreased greenness was lower than considering $PM_{2.5}$ alone. However, this result should be considered carefully due to the strong correlation between both exposures, even though it was below the threshold (spearman correlation of >0.7) which we chose as a criterion for selecting exposures for multi-pollutant models.

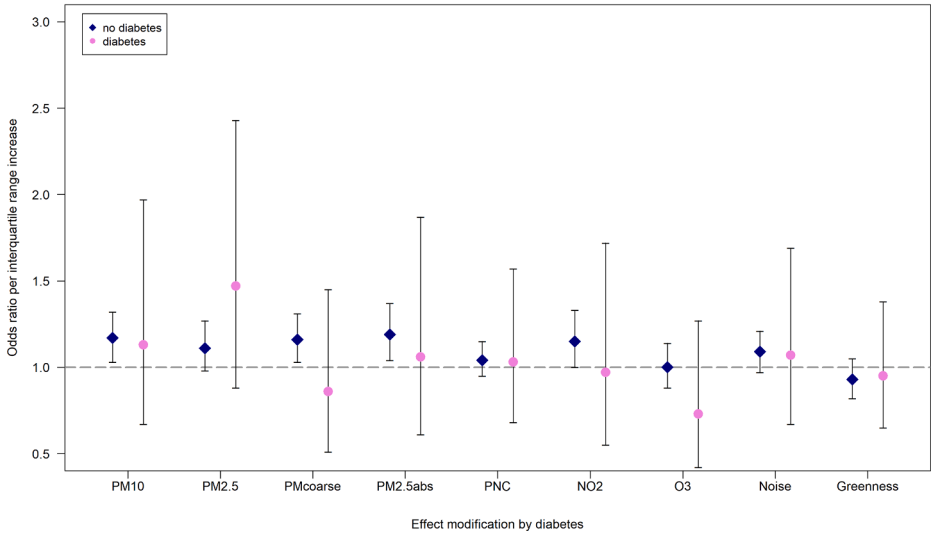
4.2.3. Effect modifications

Our results suggest a slightly stronger effect for an IQR increase in $PM_{2.5}$ for men. Lee et al. reported male sex as a potential effect modifier for the association between $PM_{2.5}$ and incident MetS, but the effect was not significant (Lee et al., 2019). Yang et al. found the same effect for prevalent MetS in the 33CCHS study, although the effect modification was not statistically significant (Yang et al., 2018). Further results by Yang et al. indicate age as a significant effect modifier for the association between residential greenness and MetS: While there was a protective effect for people aged<65 years, the association was reversed for older participants (Yang et al., 2020). This congruent to the observation we made in our stratified analysis. There is an ongoing discussion about the role of age as an effect modifier for the association between particulate matter and MetS. While there was a stronger positive association between $PM_{2.5}$ and prevalent MetS for individuals <50 years in the 33CCHS study (Yang et al., 2018), Eze et al. found stronger effects of PM_{10} for people aged >50 years (Eze et al., 2015). In our analysis, ORs for MetS per IQR increase in $PM_{2.5}$ tended to be higher for younger people <= 65 years, whereas there was no noteworthy distinction between age groups for PM_{10}.

4.3. Biological pathways

While evidence from epidemiological studies suggests that air pollution may play a role in the development of MetS, the biological mechanism remains unclear. An important factor seems to be the release of reactive oxygen species that can be induced by exposure to air pollution, leading to oxidative stress that can cause metabolic dysfunctions like chronic inflammation (Brook et al., 2010; Lodovici and Bigagli, 2011; Wei et al., 2016). $PM_{2.5}$ has been linked in studies to biomarkers of inflammation such as C-reactive protein (CRP) (Su et al., 2017; Pope et al., 2004; Zhang et al., 2017) and reduce the anti-inflammatory and anti-oxidant capacity of HDL cholesterol (Ramanathan et al., 2016). These inflammations may induce pathways that accelerate atherosclerosis (Münzel et al., 2017) and impair glucose metabolism (Liu et al., 2019). These findings are supported by epidemiological studies linking air pollution to biomarkers of insulin resistance (Kelishadi et al., 2009; Wolf et al., 2016). Furthermore, particulate matter is supposed to induce changes to the autonomic nervous system which can lead to an elevated blood pressure (Rajagopalan et al., 2018).





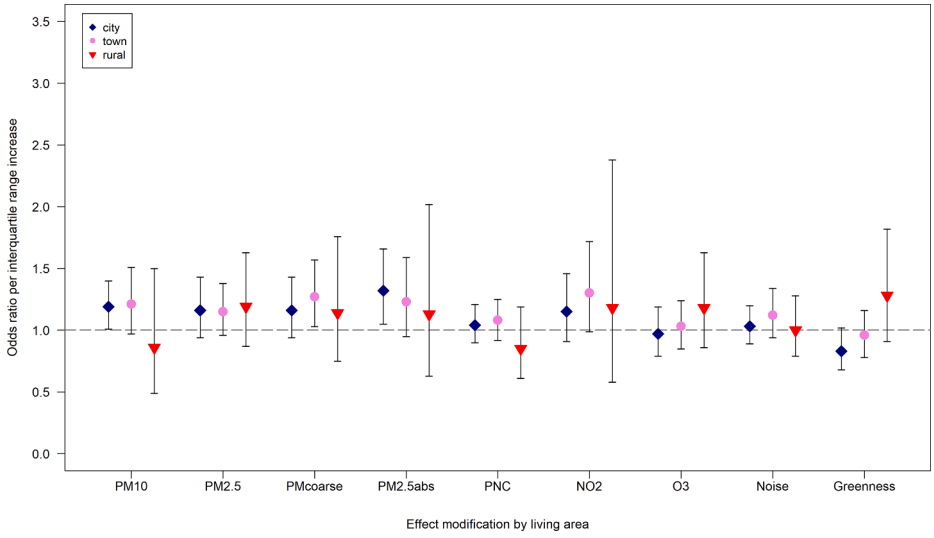


Fig. 4. (*continued*).

Similarly, different pathways are discussed for how noise might lead to cardiometabolic impairments that constitute MetS. Noise is supposed to act as an environmental stressor, causing responses of the sympathetic and endocrine system (Babisch, 2011) that include the release of stress hormones like catecholamines (Münzel et al., 2014). These can trigger physiological alterations including a rise in blood pressure and an increased heart rate that can lead to a manifestation of cardiovascular diseases (Babisch et al., 2014). Additionally, noise can disturb sleep at

night time (Miedema and Vos, 2007), which can lead to an impaired glucose metabolism (Stamatakis and Punjabi, 2010).

For greenness, the mechanisms leading to beneficial effects in health are not fully understood yet. Different biopsychological and physiological pathways are discussed. Residential greenness may act as a mitigating factor, reducing the exposure of environmental stressors like air pollution and noise. Additionally, it may help residents with restoration from stressors and help build capacities, e.g. by encouraging physical activity and social integration (Markevych et al., 2017; Kuo, 2015). These pathways are probably not independent from each other but intertwined (Hartig et al., 2014). A cross-sectional study found levels of cardiovascular risk factors such as oxidative stress in individuals living in areas with a higher NDVI (Yeager et al., 2018).

5. Strengths and limitations

This study had several strengths. We used data from the KORA cohort, a well-established study that includes a broad variety of clinical, lifestyle-related and environmental data. This allowed us to adjust for many confounders and investigate effect modifications. The longitudinal design, which was a part of our analysis, enabled us to investigate the temporal development of our outcome in dependence from the exposure variables. The results where furthermore consistent across several sensitivity analyses indicating the robustness of our findings.

There are also several limitations to this study. Our outcome was attributed to participants based on measurements taken on the day they visited the study center. This may have caused misclassifications. While trained investigators and information given to the participants should have minimized this problem, a bias may still exist. Furthermore, because estimations of air pollutants were based on measurements in 2014 and 2015, the real exposure at KORA F4, which took place from 2006 to 2008, may differ from the values used for the analysis. However, in previous studies spatial contrasts remained constant for 10 years and longer, despite changes in concentrations (Eeftens et al., 2011; Wang et al., 2013). It seems reasonable to assume that the same holds true for air pollution estimates for the period of our analysis. While exposure was assigned to home addresses of the participants, we did not measure how much time participants spent at home. Therefore, we do not know to what extent the attributed values concur with the real exposure of the subjects. Another limitation was that LUR models were calculated based on measurements from 20 monitoring sites. While LUR models have been designed with fewer stations, they tend to perform worse than LUR models with more measurement sites (Eeftens et al., 2011; Basagaña et al., 2012).

Another limitation refers to the longitudinal analysis specifically. Here, our study population underwent an extensive selection process. By excluding all participants with prevalent MetS, the selected population showed a better health status than the overall population at the time of F4: participants were on average younger and had a lower prevalence of cardiovascular risk factors. These factors may have decreased their susceptibility to the adverse cardiometabolic effects of air pollution (Liu et al., 2019; Cantone et al., 2017). However, it seems unlikely that a selection bias has led to the absence of effects in our longitudinal analysis that we were able to detect in our cross-sectional analysis. When we adjusted for MetS at the time of KORA F4, the associations between MetS at KORA FF4 and environmental exposures remained mostly unaltered.

6. Conclusion

This study showed that long-term residential exposure to PM_{10}, $PM_{2.5}$, PM_{coarse}, and $PM_{2.5}$abs is associated with a higher risk for prevalent MetS in an adult population. For incident MetS, we found no significant associations with the exposure variables. Our analysis showed no consistent results concerning vulnerable subgroups or joint influences of exposures. Our findings implicate the importance of improving air quality to prevent negative cardiometabolic health outcomes including coronary heart disease and type 2 diabetes mellitus in the general population.

CRediT authorship contribution statement

Stephan Voss: Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Alexandra Schneider:** Supervision. **Cornelia Huth:** Conceptualization. **Kathrin Wolf:** Methodology. **Iana Markevych:** Resources. **Lars Schwettmann:** Resources. **Wolfgang Rathmann:** Resources. **Annette Peters:** Resources, Supervision. **Susanne Breitner:** Conceptualization, Methodology, Formal analysis, Supervision.

Declaration of Competing Interest

The author declare that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106364.

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